REMARKS

On June 21, 2005, a Final Office Action was issued in the present case. The Office Action rejected pending claims 1, 3 and 5-12 under 35 U.S.C. §103(a) to U.S. Patent No. 6,007,690 to Nelson et al. ("Nelson") in view of Wang et al. (Rapid Communications in Mass Spectrometry) ("Wang").

With this Response, independent claim 1 has been amended to further differentiate the microfluidic device of the present invention from the cited art. As such, Applicant respectfully requests reconsideration and allowance of pending claims 1, 3 and 5-12.

Claims Rejected Under 35 U.S.C. §103(a):

The June 21, 2005 Office Action rejected claims 1, 3 and 5-12 under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 6,007,690 to Nelson et al. ("Nelson") in view of Wang et al. (Rapid Communications in Mass Spectrometry) ("Wang"), stating:

> With respect to the specifics of the membrane employed of claims 1 and 3, the reference of Nelson et al. discloses a number of possible supports that can be employed with respect to the enrichment channel (See column 6, lines 1-56). Specifically, the reference of Nelson et al. discloses the use of "ion-exchange membranes" (See column 6, lines 37-45). An ion-exchange membrane is charged and can have pores that are larger than the charged analyte that it binds with since it is merely functioning as a support matrix for binding rather than a physical particle filter. As a result, in the absence of a showing of criticality and/or unexpected results, it would have been obvious to one of ordinary skill in the art at the time the invention was made to determine the optimum material for enclosing the enrichments channel based merely on the specifics of the analyte to be reacted and/or detected in the system. (June 21, 2005 Final Office Action; Pages 3-4).

Nelson discloses a microfluidic device wherein an enrichment channel is placed in a first flow path which is substantially perpendicular to a main flow path. In Nelson, an analyte of interest is engaged to the enrichment means; after the analyte of interest has been engaged to the enrichment means, a sample is run through the main channel (which appears to be substantially perpendicular to the enrichment channel) in order to remove the analyte of interest from the

enrichment means and into the main channel. In Nelson, there is no teaching or suggestion of the benefits of concentrating the analytes at a membrane through the application of an electric field and removing the analytes from the membrane by reversing the polarity of the applied electric field. With this Response, Applicant has amended independent claim 1 in order to further illustrate the clear differences between the Nelson disclosure and the device of the pending claims.

In reviewing the Nelson disclosure, FIG. 1 shows a reverse phase material 2 located in an "enrichment channel" 10. An analyte of interest binds to the reverse phase material 2 as a sample passes along flow stream 12 to 13. As such, the analyte of interest binds to the reverse phase material 2 as a waste stream exits the enrichment channel 10 at outlet 6. Once this step is complete, an elution buffer is introduced along a flowpath of 14 to 15. "As elution buffer moves through material 2, the retained fraction of the sample is released and carried with the elution buffer out enriched fraction outlet 5 through frit 3 along flowpath 15." Nelson at Col. 11, Line 66-Col. 12, Line 5.

Each subsequent figure in Nelson shows a similar process. Further, Nelson discloses the advantages of keeping distinct main flow channels and enrichment channels. Nelson states:

> ...In the subject devices, the enrichment channel and electrophoretic flowpath are positioned such that waste fluid from the enrichment channel does not flow through the main electrophoretic flowpath, but instead flows through a discharge outlet..." (Nelson, Col. 2, Lines 53-58.)

As such, Nelson merely discloses the benefits of having two distinct channels which intersect at an enrichment material. The first channel carries the analyte of interest along with a waste material; the analyte of interest binds to the enrichment material and the waste material is allowed to pass through the channel to a waste outlet. Next, a second channel provides a buffer which carries the analyte of interest from the enrichment material to a second outlet for further processing.

In discussing the use of membranes, Nelson states:

> Alternatively, or in addition to solid phase materials such as coated particles or other insoluble matrices as the enrichment means, one may employ a coated and/or impregnated membrane which provides for selective retention of the analyte comprising fraction of the sample while allowing the remainder of the sample to flow through the membrane and out of the enrichment means through the waste outlet. A variety of hydrophilic, hydrophobic and ion-exchange membranes have been developed for use in solid phase extraction which may find use in the subject invention. See, for example, Tomlinson et al., "Novel Modifications and Clinical Applications of Preconcentration-Capillary Electrophoresis-Mass Spectrometry," J. Cap. Elect. (1995) 2: 97-104; and Tomlinson et al., "Improved On-line Membrane Preconcentration-Capillary Electrophoresis (mPC-CE),"J. High Res. Chromatogr. (1995) 18:381-3.
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> Alternatively or additionally, the enrichment channel or the enrichment medium can include a porous membrane or filter. Suitable materials for capturing genomic DNAs and viral nucleic acids include those marketed by QIAGEN under the name QIAmp, for analysis of blood, tissues, and viral RNAs; and suitable materials for capturing DNAs from plant cells and tissues include those marketed by QIAGEN under the name DNeasy.

(Nelson, Col. 6, Lines 30-53)

As such, there is no discussion of the benefits of concentrating a charged analyte at a membrane; further, there is no discussion of the use of a robust system wherein a membrane of pore size larger than that of the analyte may be used to concentrate the charged analyte at the membrane. Nelson merely discloses a membrane which allows for an analyte of interest to be retained while allowing a waste material to pass through the membrane. Next, a buffer is introduced to the Nelson device wherein the buffer carries the analyte to a second column. Nelson merely mentions that an ion exchange membrane may find use in the Nelson device.

Contrary to the Nelson device, Applicant claims a robust microfluidic device wherein a charged analyte of interest is concentrated at a membrane in a main channel. The charged analyte is delivered to the membrane by the application of an electric force. Once the analyte is concentrated at the membrane, the electric force may be reversed so as to remove the analyte of interest from the membrane. Unlike Nelson, a second column is not required. Further, the Applicant has found that through the use of an electric field, a charged analyte may be concentrated at a membrane wherein the pores of the membrane are larger in diameter than the

size of the analytes. There is no discussion of these advantages in Nelson. As such, Applicant argues that it would not have been obvious to one skilled in the art to modify the Nelson device because the Applicant has claimed a more efficient, simple, and more robust system as compared to Nelson.

In order to further distinguish the Applicant's invention from the Nelson device, the Applicant has amended independent claim 1 to require that once the charged analyte has been concentrated on the membrane, "a concentrated analyte band is removed from the membrane by reversing a polarity of an electric field." Support for the amendment may be found throughout the application as filed. More specifically:

> In one aspect of the present invention, a membrane was integrated into a microfluidic device for the purpose of concentrating analytes. In a preferred embodiment of the present invention, a nanocapillary array (or nanochannel array) is integrated into a microfluidic device for the purpose of concentrating analytes. Through the application of an electric field across the channel, charged analytes were concentrated in front of the membrane, **and a concentrated analyte band was ejected from the channel by reversing the polarity of the electric field**. In one aspect of the present invention, concentration factors up to 300-fold was measured. In one aspect of the present invention, a plurality of analytes can be concentrated in front of the same membrane without adjustments, provided that they are all anionic or cationic. In one aspect of the present invention, in the presence of an electric field a charge trapping effect was observed; small molecules can be concentrated in front of membranes with pore sizes which are orders of magnitude above the molecular weight cut-offs for hydrodynamically driven systems. Additionally, the concentrator places minimal requirements on the buffer system and is easily multiplexed.
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> For electrically driven concentration, analyte retention in front of the membrane appears to occur primarily by a charge trapping mechanism. In the presence of such a charge trapping mechanism, relatively large pores can be used to concentrate the small molecules, making the system more robust. The only known limitation to the buffer system is that the conductivity must be low enough to prevent current breakdown, and there is no need for multiple buffers or solvents which most concentrating for microfluidics and capillary electrophoresis require. Not only can this device be used for analyte concentration, but it can be used as a concentrating micro-reactor as many species can be co-localized in front

> of the membrane. With this simple and robust design, concentration factors of 300-fold have been achieved.
> (Specification, Page 10, Lines 3-25)(Emphasis added)

As such, Applicant has disclosed and claimed a microfluidic device wherein analytes of a wide range of sizes may be concentrated in front of a membrane of a large pore diameter and be subsequently removed from the membrane by changing the polarity of an applied electric field. Such a device is a clear improvement over the Nelson device because the Nelson device requires a first column to carry the analyte to an enrichment material and a second column to remove the analyte from the enrichment material. Nelson does not disclose, teach or suggest the currently claimed advantages of utilizing an electric field to concentrate an analyte in front of a membrane and removing the analyte from the membrane by merely reversing the electric field. As such, Applicant puts forth that the Nelson disclosure does not disclose, suggest or teach the Applicant's invention—a clear improvement over Nelson. As such, Applicant respectfully requests reconsideration and allowance of pending claims 1, 3, and 5-12.

Wang:

The June 21, 2005 Final Office Action cited Wang because Wang discloses, "it is conventional in the art to provide enzyme within a reaction channel on a microfluidic device." (June 21, 2005 Final Office Action; Page 3). However, Wang clearly does not cure the above-discussed deficiencies of Nelson. More specifically, Wang does not disclose a microfluidic device wherein an analyte of interest is concentrated at a membrane through the application of an electric force; further, Wang does not disclose the ability to use a membrane having pores larger than the diameter of the analyte—a benefit of the Applicant's claimed invention. Therefore, Wang does not appear to cure the deficiencies of Nelson. As such, Applicant respectfully requests reconsideration and allowance of pending claims 1, 3 and 5-12.

With this Amendment, Applicant has made an earnest effort to respond to all issues raised in the Office Action of June 21,2005, and to place all claims presented in condition for allowance. No amendment made was for the purpose of narrowing the scope of any claim, unless Applicant has argued herein that such amendment was made to distinguish over a particular reference or combination of references.

Applicant submits that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicant's attorney would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record.

Respectfully submitted,

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